Office Action Summary	Application No.	Applicant(s)	
	10/533,833	KAJINO ET AL.	
	Examiner	Art Unit	
	John Mabry, PhD	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-17,20-26 and 28* is/are pending in the application.

4a) Of the above claim(s) *9,10,18,19 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-17,20-26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant is respectfully reminded that it is required that all claims be amended to elected group. Examiner respectfully suggest Applicant amend claims to Formula I"". Examiner also warns Applicant not to introduce new matter when amending.

Examiner's Response

Applicant's response on April 4, 2008 filed in response to the Election/Restriction dated March 18, 2008 has been received and duly noted. The Examiner acknowledges Applicants' election of Group I without traverse.

Initially, Applicants' elected species did not fall within the scope of elected group. This was due to error in restriction on behalf of the Examiner. After telephonic interviews with Attorneys Dzwonczyk and Simmons, an agreement was made to revise the restricted groups and for elected species to fall within scope of Group I.

Thus, the restriction requirement is deemed proper and **FINAL**.

The revised restriction requirement is below:

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8, 11-17, 20-26 and 28 are drawn to compounds of Formula B, wherein Q2=-COR2 where R2 is unsubstituted alkyl, haloalkyl,

unsubstituted alkoxy, phenyl; Y=phenyl substituted with H, unsubstituted alkyl, halogen; Xb=piperidinyl substituted at the N-terminal with –Z-A where –Z- is unsubstituted methylene (-CH2-) or substituted with unsubstituted alkyl and –A is phenyl substituted with H, alkyl, halogen, alkoxy, haloalkylalkoxy, -S alkyl, -NHalkyl, and R1 (of Xb)=thiazolyl and imidazole substituted with H and alkyl; and compositions thereof classified in class 546, subclass 208, 209 and class 514, subclass 318. A further election of a single disclosed species is required.

II. Claims 1-8, 11-15, 19-26 and 28 are drawn to compounds of Formula B, wherein Q2=-COR2 where R2 is unsubstituted alkyl, haloalkyl, unsubstituted alkoxy, phenyl; Y=phenyl substituted with H, unsubstituted alkyl, halogen; Xb=piperidinyl substituted at the N-terminal with –Z-A where –Z- is unsubstituted methylene (-CH2-) or substituted with unsubstituted alkyl and –A is pyridinyl substituted with H, alkyl, halogen, alkoxy, haloalkylalkoxy, -S alkyl, -NHalkyl, and R1 (of Xb)= pyridinyl or –CH2-pyridinyl substituted with H, thienyl, -Salkyl, halogen and alkyl and compositions thereof classified in class 546, subclass 194 and class 514, subclass 317. A further election of a single disclosed species is required.

III. Claims 1-8, 11-26 and 28 are drawn to compounds of Formula B that are not encompassed by Groups I or II that can be classified in class 540, 544, 546 and 548, subclass dependent upon species elected. A further

election of a single disclosed species is required. This group may be subject to further restriction.

IV. Claim 9 is drawn to a method of regulating function of a neuromedin U receptor limited to the scope of one of Groups I-III, classified in class 514, dependent on the species elected. An election of a single disclosed species for use in this method is also required.

V. Claim 27 is drawn to a prodrug of Formula B limited to the scope of Groups I, II or III that can be classified in class 546, subclass variable and dependent upon species elected. A further election of a single disclosed species is required.

Note: Claim 28 is claims a medicine and for restriction purposes will be considered as a composition. Some composition claims include functional language. Regardless of function language, these claims are considered to only be composition claims.

Claim 10 is a "use" claim and has been withdrawn from examination.

In view of this response, the status of the rejections/objections of record is as follows:

Specification Objections

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title is "Receptor Regulator". Examiner suggests a title that directed towards elected group.

Claim Objections

Claim 1 is objected to because of the following informalities: The phrase "nitrogen-containing" is repeated twice on line 4 of claim 1. Appropriate correction is required.

a nitrogen-containingnitrogen-containing ring,

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "substituted" in respective claims are relative terms which renders the claim indefinite. The terms "substituted" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Oxford Dictionary of Chemistry defines the term derivative as a compound that is derived from some other compound and usually maintains its general structure.

Additionally, the term "substituted" is a relative term which renders the claim indefinite. The term "substituted" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "substituted" has no clear limitations. Where are the "metes and bounds" of the claims pertaining to the term "substituted? What does the Applicant intend by this term? Additionally, please indicate where in the Specification is such support.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble "... a pharmaceutical composition..." is vague. If applicant is claiming a pharmaceutical composition, the claim does not have a pharmaceutically acceptable carrier, excipient or diluent.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "salts", does not reasonably provide enablement for "prodrugs". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention in the instant case has claims which embrace aryl piperidine compounds. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrugs will be suitable for the instant invention.

The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by said claims. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

Claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claimed substituents (D, E R2b, R1b, Z1 and R3 of Formula I"") being unsubstituted and "optionally substituted" with unsubstituted alkyl, halo, haloakyl, unsubstited thioalkyl, cyano, and unsubstituted alkoxy, does not reasonably provide enablement for claimed substituents being "optionally substituted" by the full scope of the Specification (see pages 24-59).

The Examiner recognizes the more limited definition of the phrase "optionally substituted" on pages 60-62 as it correspond to compounds of Formula I"". As Examiner requested in an aforementioned rejection above, Applicant is strongly encouraged to limited the scope of the claims to Formula I"". The Examiner clearly expresses that the Applicant is not enabled for the full scope of "optionally substituted" in the instant application. However, the Examiner points out the Applicant is enabled for scope as described by the definition of "optionally substituted" compound of Formula I"" starting on page 60, line 12 through page 61, line 10. Examiner highly encourages Applicant to amend the claims based upon previously stated pages.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables and an unlimited number of highly substituted piperidinyl compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted piperidinyl compounds.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, steric effects, bonding, molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application's general formula I"". Pages 67, 68 and 70 of the Specification describes starting materials and methods for synthesis of compounds wherein claimed substituents are alkyl, alkoxy, halo, haloalky, cyano, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where all variables are "optionally substituted" as listed above. There is limited evidence in the Specification of the example compounds that only covers no or a small portion of the substituents claimed of formula. Thus, there is no specific direction or guidance regarding said compounds specifically mentioned in Scope.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here…As per MPEP 2164.01 (b). A key issue that can arise when

determining whether the specification is enabling is whether the starting materials or apparatus necessary to a make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

(5) State of the Prior Art: These compounds are substituted piperidinyl compounds wherein said variables are substituted with unsubstituted alky, alkoxy, halogen, trifluromethyl and cyano, which are well documented in the art. So far as the examiner is aware, no substituted piperidinyl compounds of general formula I'" where all variables are "optionally substituted" with an unlimited and undefined number of substituents. None of these kinds of structures have been made or used.

It is not trivial to experimentally interchange any and all of the many substituents that exist. As described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic

compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).

(6) Working Examples: Applicant shows example as disclosed in the Specification but no working examples were shown wherein substituted piperidinyl compounds of general formula I"'' where all variables are "optionally substituted" with an unlimited and undefined number of substituents. None of these kinds of structures have been made or used.

(7) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(8) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide,

and the lack of working examples, the Applicant has shown lack of enablement for the groups noted.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

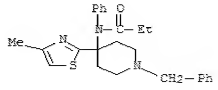
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

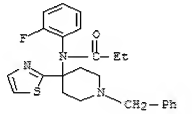
Claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al (US 4,871,749 A and US 4,791,120 A) (PTO-1449).

Lin et al discloses compounds and compositions of Formula I"" wherein R2b=ethyl, R1b= 4-methyl-2-thiazolyl, Z1=CH2 and R3=phenyl (see Example 3, column 10). Pharmaceutical compositions are taught in column 3, lines 42-42. The oxalate salts are taught in column 3, lines 50-51.



Claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Kudzma et al (J. Med. Chem. 1989, 32, 2534-42).

Lin et al discloses compounds and compositions of Formula I"" wherein R2b=ethyl, R1b= 4-methyl-2-thiazolyl, Z1=CH2 and R3=2-fluoro-phenyl (see compound 8e, page 2535, Scheme 1) (PTO-1449).



Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

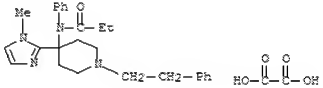
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al (US 4,831,192 A).

Scope & Content of Prior Art MPEP 2141.01

Lin et al discloses compounds and compositions of Formula I"" wherein R2b=ethyl, R1b= 1-methyl-2-imdiazol-2-yl, Z1= -CH2CH2- and R3=phenyl (see Compound 1, column 45/46). Pharmaceutical compositions are taught in column 3, line 61.



Differences between Prior Art & the Claims MPEP 2141.02

Li differs from the instant application at the -Z1R3 position: Li's -CH2CH2-phenyl versus Applicants' -CH2-phenyl. This are considered homologues. Li teaches that the -Z1 can be lower alkyl wherein the term lower alkyl means branched or unbranched containg 1-6 carbon atoms and preferably 1-4 carbon atoms (see column 3, lines 9-11 and 36-38).

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be obvious to one of ordinary skill in the art (at the time the invention

was made) to reduce the alkylene linker from -CH2CH2- to –CH2- in order to make compounds of Formula I"" as taught by Lin.

The MPEP 2144.09 which states: Compounds which are homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH_2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Applicant is respectfully reminded that it is required that all claims be amended to elected group. Examiner also warns Applicant not to introduce new matter when amending.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, PhD, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry, PhD/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625